FOXO3 Shares Common Targets with ASCL1 Genome-wide and Inhibits ASCL1-Dependent Neurogenesis.

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Public Summary:
FOXO transcription factors are central regulators of longevity from worms to humans. FOXO3, the FOXO isoform associated with exceptional human longevity, preserves adult neural stem cell pools. Here, we identify FOXO3 direct targets genome-wide in primary cultures of adult neural progenitor cells (NPCs). Interestingly, FOXO3-bound sites are enriched for motifs for bHLH transcription factors, and FOXO3 shares common targets with the proneuronal bHLH transcription factor ASCL1/MASH1 in NPCs. Analysis of the chromatin landscape reveals that FOXO3 and ASCL1 are particularly enriched at the enhancers of genes involved in neurogenic pathways. Intriguingly, FOXO3 inhibits ASCL1-dependent neurogenesis in NPCs and direct neuronal conversion in fibroblasts. FOXO3 also restrains neurogenesis in vivo. Our study identifies a genome-wide interaction between the prolongevity transcription factor FOXO3 and the cell-fate determinant ASCL1 and raises the possibility that FOXO3's ability to restrain ASCL1-dependent neurogenesis may help preserve the neural stem cell pool.

Scientific Abstract:
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